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ORIGINAL PAPER

Synthesis of azoles from 3,3′-[(4-alkoxyphenyl)imino]bis (propanoic acid hydrazides)

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Abstract Reaction of 3,3′-[(4-alkoxyphenyl)imino]bis (propanoic acid hydrazides) with CS_2 in alkaline solution and subsequent acidification gave 5,5′-[[(4-alkoxyphenyl)imino]diethane-2,1-diyl]bis(1,3,4-oxadiazole-2(3*H*)-thiones). The same dihydrazides on reaction with phenyl isocyanates or phenyl isothiocyanates were converted to bis[*N*′-(phenylaminocarbonyl)propanoic acid hydrazides] and bis[*N*′-(phenylaminocarbonothioyl)propanoic acid hydrazides], which underwent cyclization in alkaline medium to produce 5,5′-[[(4-alkoxyphenyl)imino]diethane-2,1-diyl]bis(4-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones) and their 3-thio analogues, whereas in sulfuric acid or $POCl_3$ 5,5′-[[(4-alkoxyphenyl)imino]diethane-2,1-diyl] bis(*N*-phenyl-1,3,4-oxadiazol-2-amines) and 5,5′-[[(4-alkoxyphenyl)imino]diethane-2,1-diyl]bis(*N*-phenyl-1,3,4-thiadiazol-2-amines) were obtained.

Keywords Dihydrazides · Hydrazinocarboxamides · 1,3,4-Oxadiazoles · 1,3,4-Thiadiazoles · 1,2,4-Triazoles

Introduction

Heterocyclic compounds are of particular importance among pharmaceutically and biologically active compounds. Five-membered heterocyclic compounds, triazoles, oxazoles, and thiazoles, have a broad spectrum of biological activity. 1,2,4-Triazoles and 1,3,4-oxadiazoles are known for their anti-inflammatory [1], antibacterial [2, 3], and antimicrobial [4] effect. The triazole system is a structural element of many drugs [5]. Cyclization of hydrazine derivatives is a widely known method for synthesis of diazoles.

N-Substituted 3-amino acids and their derivatives elicit a broad spectrum of biological activity [6–8], therefore, in this work 3,3′-[(4-alkoxyphenyl)imino]bis(propanoic acid hydrazides) were used for the synthesis of compounds containing two oxadiazole, thiadiazole, or triazole rings in their structure.

Results and discussion

Reaction of alkoxydithioformate with hydrazide [9] was adopted for the synthesis of compounds **2** containing two 1,3,4-oxadiazol-2-thione fragments. 5,5′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis(1,3,4-oxadiazole-2(3*H*)-thione) (**2a**) and its 4-ethoxy homologue **2b** were prepared [9] in 57–65% yield by heating under reflux the corresponding hydrazides **1** with carbon disulfide in basic medium and subsequent cyclization, in situ with hydrochloric acid, of the potassium salts of hydrazinocarbodithioates formed. Methanol and ethanol were tested as solvents for this reaction. The better yields of **2** were obtained in ethanol. The ^{13}C NMR spectra of these compounds exhibited carbon resonances at 162.79–162.82 ppm confirming the presence of the C=N fragment of the oxadiazole ring (Scheme 1).

Hydrazinocarboxamides undergo cyclization in phosphoryl chloride or sulfuric acid [9], forming 1,3,4-oxadiazole derivatives. Reaction of dihydrazides **1** with phenyl or 4-chlorophenyl isocyanates, or phenyl isothiocyanate in methanol gave hydrazinocarboxamides **3** and **4**, and hydrazinocarbothiamide derivatives **5**, cyclization of which in basic medium resulted in 5,5′-[[(4-methoxyphenyl)

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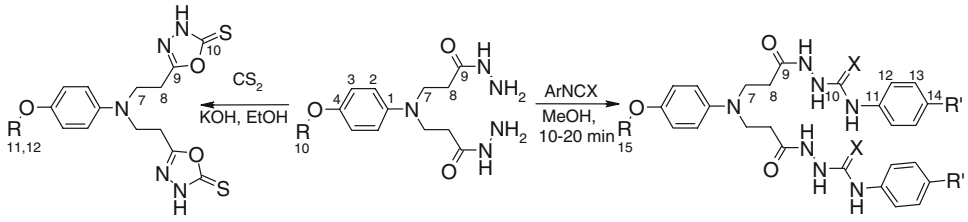
Scheme 1



2a R = Me
2b R = Et

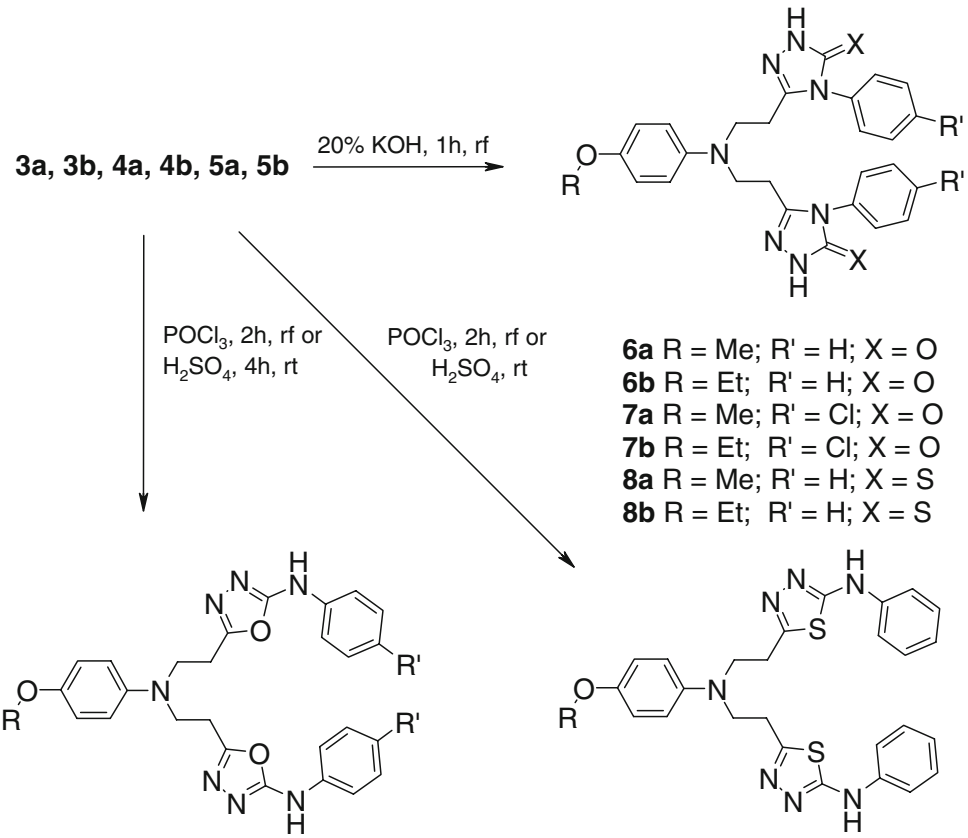
1a R = Me
1b R = Et

3a R = Me; R' = H; X = O
3b R = Et; R' = H; X = O
4a R = Me; R' = Cl; X = O
4b R = Et; R' = Cl; X = O
5a R = Me; R' = H; X = S
5b R = Et; R' = H; X = S

imino]diethane-2,1-diyl]bis(4-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones) **6a**, **7a** or their ethoxy derivatives **6b**, **7b**, and the thio analogues **8**. In the reaction of dihydrazides **3**–**5** with phenyl isocyanate, crystals of the semicarbazides began to appear after heating for 10 min, whereas for phenyl isothiocyanate more prolonged heating was required (Scheme 2).

The ^{1}H NMR spectra of semicarbazides **3** and **4** and thiosemicarbazide **5** showed a set of signals for the protons of the phenyl residue, whereas the signals of the primary amino group present in the hydrazide **1** were absent. The triazole ring proved to have a marked deshielding effect on the hydrogen atoms of the neighboring methylene group, as a result of which the signals in the ^{1}H NMR spectra of **6**–**8** are found shifted down-field by 0.19 and 0.31 ppm in comparison with the corresponding signals in the spectra of the starting dihydrazides **1** [8].

Scheme 2



6a R = Me; R' = H; X = O
6b R = Et; R' = H; X = O
7a R = Me; R' = Cl; X = O
7b R = Et; R' = Cl; X = O
8a R = Me; R' = H; X = S
8b R = Et; R' = H; X = S

9a R = Me; R' = H
9b R = Et; R' = H
10a R = Me; R' = Cl
10b R = Et; R' = Cl

11a R = Me
11b R = Et

Thus, 5,5′-[[(4-methoxyphenyl)imino]diethane-2,1-diyl] bis(*N*-phenyl-1,3,4-oxadiazol-2-amine) (**9a**), its ethoxy analogue **9b**, and chloro derivatives **10** were synthesized by heating under reflux hydrazinocarboxamides **3** and **4** in phosphoryl chloride or keeping them in sulfuric acid. Under the same conditions, thiadiazole derivatives **11** were obtained from hydrazinocarbothiamides **5**. In the ^{1}H NMR spectra of **9–11** the proton signals of the CONHNH group are absent in comparison with the spectra for **3–5**. Mass spectra of all synthesized compounds **2–11** showed molecular ion peaks.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 spectrometer (300 and 75 MHz) using TMS as an internal standard and DMSO-d_6 as a solvent. IR spectra were taken on a Perkin–Elmer Spectrum Bx FT-IR spectrometer. Mass spectra were recorded on a Waters Micromass ZQ 2000 instrument using chemical ionization. Elemental analyses (C, H, N) were performed on an Elemental Analyzer CE-440, and the results were found to be in good agreement (±0.2%) with the calculated values. Melting points were determined on the Auto probe analyzer APA 1. Monitoring of the reaction course and purity of the compounds prepared was carried out using TLC on Silufol 254 and Silufol UV-254 plates.

5,5′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]-bis(1,3,4-oxadiazole-2(3H)-thione) (**2a**, $C_{15}H_{17}N_5O_3S_2$)
To a solution of 2.8 g KOH in 75 cm^3 EtOH 4.5 cm^3 CS_2 (5.7 g, 75 mmol) was added drop-wise and stirred for 15 min at 20 °C. To this solution 7.37 g **1a** (25 mmol) in 50 cm^3 EtOH was added and the mixture was stirred at reflux for 20 h. The liquid fraction was removed under vacuo, the residue was dissolved in 75 cm^3 H_2O, HCl was added to pH 3–4, and the slurry formed was separated, washed with water and crystallized from methanol to give 5.9 g (65%) **2a**. M.p.: 108–109 °C; ^{1}H NMR: $\delta = 2.91$ (t, 4H, $J = 6.9$ Hz, CH_2C=N), 3.61 (t, 4H, $J = 6.9$ Hz, CH_2N), 3.69 (s, 3H, CH_3O), 6.78–6.85 (m, 4H, HAr), 9.93, 10.08 (2 s, 2H, NH) ppm; ^{13}C NMR: $\delta = 177.74$ (C-10), 162.79 (C-9), 141.74 (C-1), 115.41 (C-3, 5), 151.45 (C-4), 114.74 (C-2, 6), 55.22 (C-11), 47.24 (C-7), 32.49 (C-8) ppm; IR (KBr): $\bar{\nu} = 3{,}171$ (NH), 1,512 (C=S) cm^{-1}; MS (20 eV): *m/z* (%) = 380 ([M + H]$^+$, 100).

5,5′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-(1,3,4-oxadiazole-2(3H)-thione) (**2b**, $C_{16}H_{19}N_5O_3S_2$)
Prepared similarly to **2a** from 3 cm^3 (3.8 g, 50 mmol) CS_2 and 7.73 g **1b** (25 mmol). Crystallization from methanol afforded 6.83 g (57%) **2b**. M.p.: 125–126 °C; ^{1}H NMR: $\delta = 1.26$ (t, 3H, $J = 6.9$ Hz, *CH*$_3$CH$_2$O), 2.26 (t, 4H, $J = 7.5$ Hz; CH_2C=N), 3.40 (t, 4H, $J = 7.5$ Hz, CH_2N), 3.88 (q, 2H, $J = 6.9$ Hz, CH_3*CH*$_2$O), 6.59 (d, 2H, $J = 9.3$ Hz, $H_{(2,6)}$Ar), 6.75 (d, 2H, $J = 9.3$ Hz, $H_{(3,5)}$Ar), 8.16 (br s, 2H, NH) ppm; ^{13}C NMR: $\delta = 174.90$ (C-10), 162.82 (C-9), 149.54 (C-4), 142.06 (C-1), 115.41 (C-3, 5), 113.34 (C-2, 6), 63.22 (C-12), 47.63 (C-7), 34.13 (C-8), 14.83 (C-11) ppm; IR (KBr): $\bar{\nu} = 3{,}171$ (NH), 1,507 (C=S) cm^{-1}; MS (15 eV): *m/z* (%) = 394 ([M + H]$^+$, 50).

3,3′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis-[N′-(phenylaminocarbonyl)propanoic acid hydrazide] (**3a**, $C_{27}H_{31}N_7O_5$)
To a hot solution of 1.47 g **1a** (5 mmol) in 50 cm^3 MeOH 1.19 cm^3 phenyl isocyanate (10 mmol) was added. The mixture was heated under reflux until a precipitate appeared (10 min) and cooled. The crystals were isolated by filtration, washed with methanol, and recrystallized from DMF–H_2O to afford 1.9 g (71%) **3a**. M.p.: 200–201 °C; ^{1}H NMR: $\delta = 2.40$ (t, 4H, $J = 7.2$ Hz, CH_2CO), 3.51 (t, 4H, $J = 7.2$ Hz, CH_2N), 3.69 (s, 3H, CH_3O), 6.75 (d, 2H, $J = 7.2$ Hz, $H_{(2,6)}$Ar), 6.86 (d, 2H, $J = 7.2$ Hz, $H_{(3,5)}$Ar), 7.24–7.46 (m, 10H, H–Ar′), 8.04, 8.71 (2s, 4H, *NHNH*CO), 9.73 (s, 2H, NHAr′) ppm; ^{13}C NMR: $\delta = 170.67$ (C-9), 155.18 (C-10), 151.12 (C-4), 141.49 (C-1), 139.49 (C-11), 128.54 (C-13, 15), 121.78 (C-12, 16), 118.36 (C-14), 114.74 (C-3, 5), 114.36 (C-2, 6), 55.24 (C-17), 47.14 (C-7), 31.24 (C-8) ppm; IR (KBr): $\bar{\nu} = 1{,}660$ (C=O) cm^{-1}; MS (ESI, 20 eV): *m/z* (%) = 534 ([M + H]$^+$, 100).

3,3′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-[N′-(phenylaminocarbonyl)propanoic acid hydrazide] (**3b**, $C_{28}H_{33}N_7O_5$)
Prepared similarly to **3a** from 3.09 g **1b** (10 mmol) and 2.38 cm^3 phenyl isocyanate (20 mmol). Recrystallization from DMF–H_2O afforded 3.98 g (75%) **3b**. M.p.: 201–202 °C; ^{1}H NMR: $\delta = 1.27$ (t, 3H, $J = 6.9$ Hz, *CH*$_3$CH$_2$O), 2.38 (t, 4H, $J = 6.9$ Hz, CH_2CO), 3.40 (q, 2H, $J = 6.9$ Hz, CH_3*CH*$_2$O), 3.55 (t, 4H, $J = 7.2$ Hz, CH_2N), 6.77 (d, 2H, $J = 8.5$ Hz, $H_{(2,6)}$Ar), 7.00 (d, 2H, $J = 8.5$ Hz, $H_{(3,5)}$Ar), 7.17–7.47 (m, 10H, H–Ar′), 7.99 (s, 2H, NH*NH*CO), 8.67 (s, 2H, *NH*NHCO), 9.70 (s, 2H, NHAr) ppm; ^{13}C NMR: $\delta = 170.15$ (C-9), 155.39 (C-10), 141.59 (C-1), 139.02 (C-11), 115.67 (C-3, 5), 128.11 (C-13), 151.14 (C-4), 129.21 (C-14), 115.89 (C-12), 114.32 (C-2, 6), 63.31 (C-17), 47.48 (C-7), 31.45 (C-8), 14.87 (C-18) ppm; IR (KBr): $\bar{\nu} = 1{,}676$ (C=O) cm^{-1}; MS (ESI, 20 eV): *m/z* (%) = 548 ([M + H]$^+$, 80).

3,3′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis-[N′-[(4-chlorophenyl)aminocarbonyl]propanoic acid hydrazide] (**4a**, $C_{27}H_{29}Cl_2N_7O_5$)
Prepared similarly to **3a** from 2.95 g **1a** (10 mmol) and 3.07 cm^3 4-chlorophenyl isocyanate (20 mmol). Recrystallization from DMF–H_2O afforded 5.9 g (98%) **4a**. M.p.: 219–

220 °C; ^{1}H NMR: $\delta = 2.39$ (t, 4H, $J = 7.2$ Hz, $COCH_2$), 3.49 (t, 4H, $J = 7.2$ Hz, CH_2N), 3.67 (s, 3H, CH_3O), 6.73 (d, 2H, $J = 9.3$ Hz, $H_{(2,6)}Ar$), 6.83 (d, 2H, $J = 9.3$ Hz, $H_{(3,5)}Ar$), 7.29 (d, 4H, $J = 6.9$ Hz, $H_{(3,5)}Ar'$), 7.47 (d, 4H, $J = 6.9$ Hz, $H_{(2,6)}Ar'$), 8.12, 8.86 (2s, 4H, *NHNH*CO), 9.73, 9.80 (2s, 2H, NHAr′) ppm; ^{13}C NMR: $\delta = 170.63$ (C-9), 155.41 (C-10), 150.60 (C-4), 141.65 (C-1), 138.49 (C-11), 138.25 (C-14), 128.21 (C-13, 15), 125.41 (C-12, 16), 115.25 (C-3, 5), 113.73 (C-2, 6), 55.35 (C-17), 46.53 (C-7), 31.92 (C-8) ppm; IR (KBr): $\bar{\nu}$ = 3,360, 3,341 (NH), 1,640 (C=O) cm^{-1}; MS (ESI, 20 eV): *m/z* (%) = 603 ($[M + H]^+$, 60).

3,3′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-[N′-[(4-chlorophenyl)aminocarbonyl]propanoic acid hydrazide] (**4b**, $C_{28}H_{31}Cl_2N_7O_5$)

Prepared similarly to **4a** from 3.09 g **1b** (10 mmol) and 3.07 cm^3 4-chlorophenyl isocyanate (20 mmol). Recrystallization from DMF–H_2O afforded 5.24 g (85%) **4b**. M.p.: 201–202 °C; ^{1}H NMR: $\delta = 1.29$ (t, 3H, $J = 6.9$ Hz, CH_3CH_2O), 2.41 (t, 4H, $J = 7.2$ Hz, $COCH_2$), 3.50 (t, 4H, $J = 7.2$ Hz, CH_2N), 3.99 (q, 2H, $J = 6.9$ Hz, CH_3CH_2O), 6.69 (d, 2H, $J = 9.3$ Hz, $H_{(2,6)}Ar$), 6.89 (d, 2H, $J = 9.3$ Hz, $H_{(3,5)}Ar$), 7.35 (d, 4H, $J = 6.9$ Hz, $H_{(3,5)}Ar'$), 7.52 (d, 4H, $J = 6.9$ Hz, $H_{(2,6)}Ar'$), 8.10, 8.75 (2s, 4H, *NHNH*CO), 9.74, 9.89 (2 s, 2H, NHAr′) ppm; ^{13}C NMR: $\delta = 171.02$ (C-9), 156.11 (C-10), 150.63 (C-4), 141.69 (C-1), 138.53 (C-11), 138.28 (C-14), 128.37 (C-13, 15), 125.53 (C-12, 16), 115.41 (C-3, 5), 113.53 (C-2, 6), 55.34 (C-17), 46.53 (C-7), 24.82 (C-8), 17.08 (C-18) ppm; IR (KBr): $\bar{\nu}$ = 3,355, 3,324 (NH), 1,643 (C=O) cm^{-1}; MS (ESI, 20 eV): *m/z* (%) = 617 ($[M + H]^+$, 70).

3,3′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis-[N′-(phenylaminocarbonothioyl)propanoic acid hydrazide] (**5a**, $C_{27}H_{31}N_7O_3S_2$)

To a solution of 3 g **1a** (10 mmol) in 80 cm^3 MeOH was added 2.4 cm^3 (2.7 g, 20 mmol) phenyl isothiocyanate and the reaction mixture was heated under reflux for 4 h. It was cooled, Et_2O was added, and the crystals were isolated by filtration. Recrystallization from DMF–H_2O afforded 3.9 g (69%) **5a**. M.p.: 110–111 °C; ^{1}H NMR: $\delta = 2.42$ (t, 4H, $J = 7.2$ Hz, CH_2CO), 3.50 (t, 4H, $J = 7.2$ Hz, CH_2N), 3.67 (s, 3H, CH_3O), 6.75 (d, 2H, $J = 9.3$ Hz, $H_{(2,6)}Ar$), 6.83 (d, 2H, $J = 9.3$ Hz, $H_{(3,5)}Ar$), 7.16 (t, 2H, $J = 7.2$ Hz, $H_{(4)}Ar'$), 7.33 (t, 4H, $J = 7.2$ Hz, $H_{(3,5)}Ar'$), 7.42 (d, 4H, $J = 7.2$ Hz, $H_{(2,6)}Ar'$), 9.55 (s, 4H, *NHNH*CO), 9.95 (s, 2H, NHAr′) ppm; ^{13}C NMR: $\delta = 180.97$ (C-10), 170.57 (C-9), 151.27 (C-4), 141.55 (C-1), 139.01 (C-11), 128.90 (C-14), 128.00 (C-13, 15), 125.06 (C-12, 16), 114.73 (C-2, 6), 114.19 (C-3, 5), 55.25 (C-17), 46.94 (C-7), 31.26 (C-8) ppm; IR (KBr): $\bar{\nu}$ = 1,701 (C=O), 1,110 (C=S) cm^{-1}; MS (ESI, 20 eV): *m/z* (%) = 566 ($[M + H]^+$, 100).

3,3′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-[N′-(phenylaminocarbonothioyl)propanoic acid hydrazide] (**5b**, $C_{28}H_{33}N_7O_3S_2$)

Prepared similarly to **5a** from 3.1 g **1b** (10 mmol) and 2.4 cm^3 phenyl isothiocyanate (2.7 g, 20 mmol). Recrystallization from DMF–H_2O afforded 4.1 g (71%) **5b**. M.p.: 133–134 °C; ^{1}H NMR: $\delta = 1.37$ (t, 3H, $J = 6.9$ Hz, CH_3CH_2O), 3.48 (t, 4H, $J = 6.9$ Hz, CH_2O), 3.59 (t, 4H, $J = 6.9$ Hz, CH_2N), 3.99 (q, 2H, $J = 6.9$ Hz, CH_3CH_2O), 6.83 (d, 2H, $J = 9.3$ Hz, $H_{(2,6)}Ar$), 6.91 (d, 2H, $J = 9.3$ Hz, $H_{(3,5)}Ar$), 7.25 (t, 2H, $J = 7.2$ Hz, $H_{(4)}Ar'$), 7.42 (t, 4H, $J = 7.2$ Hz, $H_{(3,5)}Ar'$), 7.49 (d, 4H, $J = 7.2$ Hz, $H_{(2,6)}Ar'$), 9.67 (s, 4H, *NHNH*CO), 10.07 (br s, 2H, NHAr′) ppm; ^{13}C NMR: $\delta = 181.08$ (C-10), 170.59 (C-9), 150.45 (C-4), 141.50 (C-1), 139.01 (C-11), 129.45 (C-14), 128.00 (C-13, 15), 125.04 (C-12, 16), 115.45 (C-3, 5), 114.67 (C-2, 6), 63.24 (C-17), 46.95 (C-7), 31.28 (C-8), 14.76 (C-18) ppm; IR (KBr): $\bar{\nu}$ = 1,690 (C=O), 1,105 (C=S) cm^{-1}; MS (ESI, 20 eV): *m/z* (%) = 580 ($[M + H]^+$, 100).

5,5′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis-(4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one) (**6a**, $C_{27}H_{27}N_7O_3$)

A solution of 0.53 g **3a** (1 mmol) in 20 cm^3 20% KOH solution was heated under reflux for 1 h. The reaction mixture was cooled, conc. HCl was added to pH 4, and the precipitated crystals were isolated by filtration and washed with water. Recrystallization from DMF–H_2O afforded 0.34 g (68%) **6a**. M.p.: 190–191 °C; ^{1}H NMR: $\delta = 2.70$ (t, 4H, $J = 8.1$ Hz, $CH_2C{=}N$), 3.45 (t, 4H, $J = 8.1$ Hz, CH_2N), 3.78 (s, 3H, CH_3O), 6.05 (d, 2H, $J = 9$ Hz, $H_{(2,6)}Ar$), 6.55 (t, 2H, $J = 9$ Hz, $H_{(3,5)}Ar$), 7.32–7.51 (m, 10H, H–Ar′), 11.74 (s, 2H, NH) ppm; ^{13}C NMR: $\delta = 154.21$ (C-10), 150.79 (C-4), 145.01 (C-9), 140.44 (C-1), 132.72 (C-11), 129.41 (C-14), 128.62 (C-13, 15), 127.44 (C-12, 16), 114.61(C-3, 5), 113.11 (C-2, 6), 55.17 (C-17), 47.28 (C-7), 23.61 (C-8) ppm; MS (ESI, 20 eV): *m/z* (%) = 498 ($[M + H]^+$, 45).

5,5′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-(4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one) (**6b**, $C_{28}H_{29}N_7O_3$)

Prepared similarly to **6a** from 1.37 g **3b** (2.5 mmol). Recrystallization from DMF–H_2O afforded 1.06 g (74%) **6b**. M.p.: 197–198 °C; ^{1}H NMR: $\delta = 1.27$ (t, 3H, $J = 6.9$ Hz, CH_3CH_2O), 2.50 (t, 4H, $J = 8.1$ Hz, $CH_2C{=}N$), 3.20 (t, 4H, $J = 8.1$ Hz, CH_2N), 3.92 (q, 2H, $J = 6.9$ Hz, CH_3CH_2O), 6.78 (d, 2H, $J = 9$ Hz, $H_{(2,6)}Ar$), 6.99 (t, 2H, $J = 9$ Hz, $H_{(3,5)}Ar$), 7.29–7.52 (m, 10H, H–Ar′), 11.79 (s, 2H, NH) ppm; MS (20 eV): *m/z* (%) = 512 ($[M + H]^+$, 65).

5,5′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis-[4-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one] (**7a**, $C_{27}H_{25}Cl_2N_7O_3$)

Prepared similarly to **6a** from 1.202 g **4a** (2 mmol). Recrystallization from DMF–H_2O afforded 0.5 g (44%) **7a**. M.p.: 251–252 °C; ^{1}H NMR: $\delta = 2.23$ (t, 4H, $J = 7.2$ Hz, CH_2C=N), 3.23 (t, 4H, $J = 7.2$ Hz, CH_2N), 3.63 (s, 3H, CH_3O), 6.02 (d, 2H, $J = 9.2$ Hz, $H_{(2,6)}$Ar), 6.57 (d, 2H, $J = 9.2$ Hz, $H_{(3,5)}$Ar), 7.39 (d, 4H, $J = 6.9$ Hz, $H_{(3,5)}$Ar′), 7.57 (d, 4H, $J = 6.9$ Hz, $H_{(2,6)}$Ar′), 11.78 (s, 2H, NH) ppm; ^{13}C NMR: $\delta = 154.98$ (C-10), 150.62 (C-4), 145.35 (C-9), 141.67 (C-1), 138.50 (C-11), 138.39 (C-14), 128.80 (C-13, 15), 125.56 (C-12, 16), 115.26 (C-3, 5), 113.89 (C-2, 6), 55.37 (C-17), 46.54 (C-7), 31.95 (C-8) ppm; MS (20 eV): *m/z* (%) = 567 ($[M + H]^+$, 70).

5,5′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-[4-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one] (**7b**, $C_{28}H_{27}Cl_2N_7O_3$)

Prepared similarly to **7a** from 1.23 g **4b** (2 mmol). Recrystallization from DMF–H_2O afforded 0.64 g (55%) **7b**. M.p.: 229–230 °C; ^{1}H NMR: $\delta = 1.28$ (t, 3H, $J = 7.2$ Hz, CH_3CH_2O), 2.53 (t, 4H, $J = 7.2$ Hz, CH_2C=N), 3.24 (t, 4H, $J = 7.2$ Hz, CH_2N), 3.89 (q, 2H, $J = 7.2$ Hz, CH_3CH_2O), 6.04 (d, 2H, $J = 9.0$ Hz, $H_{(2,6)}$Ar), 6.58 (d, 2H, $J = 9.0$ Hz, $H_{(3,5)}$Ar), 7.41 (d, 4H, $J = 8.7$ Hz, $H_{(3,5)}$Ar′), 7.58 (d, 4H, $J = 8.7$ Hz, $H_{(2,6)}$Ar′), 11.78 (s, 2H, NH) ppm; ^{13}C NMR: $\delta = 154.02$ (C-10), 150.00 (C-4), 144.90 (C-9), 140.21 (C-1), 133.19 (C-11), 131.62 (C-12, 16), 129.39 (C-14), 129.24 (C-13, 15), 115.16 (C-3, 5), 113.09 (C-2, 6), 63.11 (C-17), 47.41 (C-7), 23.54 (C-8), 14.72 (C-18) ppm; MS (20 eV): *m/z* (%) = 581 ($[M + H]^+$, 100).

5,5′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis-(4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-thione) (**8a**, $C_{27}H_{27}N_7OS_2$)

Compound **5a** (0.28 g, 0.5 mmol) was dissolved in 20 cm^3 20% KOH solution and heated under reflux for 1 h. After cooling the reaction mixture to room temperature acetic acid was added to pH 4, the precipitated crystals were isolated by filtration and washed with water. Recrystallization from methanol afforded 0.21 g (81%) **8a**. M.p.: 245–246 °C; ^{1}H NMR: $\delta = 2.24$ (t, 4H, $J = 7.05$ Hz, CH_2C=N), 3.63 (t, 4H, $J = 7.05$ Hz, CH_2N), 3.67 (s, 3H, CH_3O), 6.05 (d, 2H, $J = 7.2$ Hz, $H_{(2,6)}$Ar), 6.69 (d, 2H, $J = 7.2$ Hz, $H_{(3,5)}$Ar), 7.46–7.61 (m, 10H, H–Ar′), 13.79 (s, 2H, NH) ppm; ^{13}C NMR: $\delta = 180.97$ (C-10), 170.57 (C-9), 151.27 (C-4), 141.55 (C-1), 139.00 (C-11), 128.90 (C-14), 128.00 (C-13, 15), 125.06 (C-12, 16), 114.73 (C-3, 5), 114.19 (C-2, 6), 55.25 (C-17), 46.94 (C-7), 31.26 (C-8) ppm; IR (KBr): $\bar{\nu}$ = 3,310 (NH), 1,520, 1,460 (CS) cm^{-1}; MS (70 eV): *m/z* (%) = 530 ($[M + H]^+$, 80).

5,5′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-(4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-thione) (**8b**, $C_{28}H_{29}N_7OS_2$)

Prepared similarly to **8a** from 1.37 g **5b** (2.5 mmol). Recrystallization from DMF–H_2O afforded 1.06 g (78%) **8b**. M.p.: 236–237 °C; ^{1}H NMR: $\delta = 1.25$ (t, 3H, $J = 6.9$ Hz, CH_3CH_2O), 2.53 (t, 4H, $J = 6.9$ Hz, CH_2C=N), 3.24 (t, 4H, $J = 6.9$ Hz, CH_2N), 3.85 (q, 2H, $J = 6.9$ Hz, CH_3CH_2O), 5.97 (d, 2H, $J = 9$ Hz, $H_{(2,6)}$Ar), 6.52 (d, 2H, $J = 9$ Hz, $H_{(3,5)}$Ar), 7.36–7.56 (m, 10H, H–Ar′), 13.79 (s, 2H, NH) ppm; ^{13}C NMR: $\delta = 167.51$ (C-10), 150.26 (C-4), 150.09 (C-9), 141.73 (C-1), 140.09 (C-11), 133.51 (C-14), 129.44 (C-13, 15), 128.30 (C-12, 16), 115.29 (C-3, 5), 113.13 (C-2, 6), 63.14 (C-17), 47.51 (C-7), 23.20 (C-8), 14.74 (C-18) ppm; IR (KBr): $\bar{\nu}$ = 3,190 (NH) cm^{-1}; MS (70 eV): *m/z* (%) = 544 ($[M + H]^+$, 90).

5,5′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis-(N-phenyl-1,3,4-oxadiazol-2-amine) (**9a**, $C_{27}H_{27}N_7O_3$)

A mixture of 0.53 g **3a** (1 mmol) in 10 cm^3 $POCl_3$ was heated under reflux for 2 h, cooled and added drop-wise to ice. The precipitate was isolated by filtration and washed with water. Recrystallization from DMF–H_2O afforded 0.39 g (79%) **9a**. M.p.: 179–180 °C; ^{1}H NMR: $\delta = 2.70$ (t, 4H, $J = 8.1$ Hz, CH_2C=N), 3.45 (t, 4H, $J = 8.1$ Hz, CH_2N), 3.79 (s, 3H, CH_3O), 6.93 (d, 2H, $J = 7.2$ Hz, $H_{(2,6)}$Ar), 7.06 (t, 2H, $J = 7.2$ Hz, $H_{(3,5)}$Ar), 7.23–7.58 (m, 10H, H–Ar′), 9.77, 9.92 (2s, 2H, NH) ppm; IR (KBr): $\bar{\nu}$ = 3,202 (NH), 1,628 (C=N) cm^{-1}; MS (70 eV): *m/z* (%) = 498 ($[M + H]^+$, 60).

5,5′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-(N-phenyl-1,3,4-oxadiazol-2-amine) (**9b**, $C_{28}H_{29}N_7O_3$)

A mixture of 1.36 g **3b** (2.5 mmol) and 5 cm^3 H_2SO_4 was stirred at room temperature for 4 h. The reaction mixture was cooled and added drop-wise to ice. The precipitate was isolated by filtration and washed with water. Recrystallization from DMF–H_2O afforded 1.03 g (81%) **9b**. M.p.: 202–203 °C; ^{1}H NMR: $\delta = 1.34$ (t, 3H, $J = 6.9$ Hz, CH_3CH_2O), 2.35 (t, 4H, $J = 6.9$ Hz, CH_2CO), 3.87 (t, 4H, $J = 6.9$ Hz, CH_2N), 4.08 (q, 2H, $J = 6.9$ Hz, CH_3CH_2O), 6.95 (d, 2H, $J = 9.2$ Hz, $H_{(2,6)}$Ar), 7.13 (d, 2H, $J = 9.2$ Hz, $H_{(3,5)}$Ar), 7.29 (t, 2H, $J = 7.2$ Hz, $H_{(4)}$Ar′), 7.37 (t, 4H, $J = 7.2$ Hz, $H_{(3,5)}$Ar′), 7.50 (d, 4H, $J = 7.2$ Hz, $H_{(2,6)}$Ar′), 9.78 (s, 2H, NHAr′) ppm; ^{13}C NMR: $\delta = 168.65$ (C-10), 155.09 (C-4), 154.93 (C-9), 141.54 (C-1), 139.96 (C-11), 126.08 (C-13, 15), 123.84 (C-14), 117.48 (C-12, 16), 117.33 (C-2, 6), 115.89 (C-3, 5), 63.66 (C-17), 47.75 (C-7), 28.53 (C-8), 14.47 (C-18) ppm; IR (KBr): $\bar{\nu}$ = 3,289 (NH), 1,707 (C=N) cm^{-1}; MS (20 eV): *m/z* (%) = 512 ($[M + H]^+$, 100).

5,5′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis-[N-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine]
(**10a**, $C_{27}H_{25}Cl_2N_7O_3$)
Prepared similarly to **9b** from 1.202 g **4a** (2 mmol). Recrystallization from DMF–H_2O afforded 0.56 g (50%) **10a**. M.p.: 226–227 °C; ^{1}H NMR: $\delta = 2.36$ (t, 4H, $J = 6.9$ Hz, CH_2CO), 3.65 (s, 3H, CH_3O), 3.86 (t, 4H, $J = 6.9$ Hz, CH_2N), 7.15 (d, 2H, $J = 9.2$ Hz, $H_{(2,6)}Ar$), 7.29 (d, 2H, $J = 9.2$ Hz, $H_{(3,5)}Ar$), 7.45 (d, 4H, $J = 7.2$ Hz, $H_{(3,5)}Ar'$), 7.61 (d, 4H, $J = 7.2$ Hz, $H_{(2,6)}$ Ar'), 9.76 (s, 2H, $NHAr'$) ppm; ^{13}C NMR: $\delta = 168.85$ (C-10), 160.00 (C-9), 155.06 (C-4), 154.05 (C-1), 138.69 (C-11), 138.22 (C-14), 128.72 (C-13, 15), 123.94 (C-2, 6), 119.77 (C-12, 16), 115.68 (C-3, 5), 55.78 (C-17), 51.85 (C-7), 28.49 (C-8) ppm; MS (20 eV): *m/z* (%) = 567 ($[M + H]^+$, 100).

5,5′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-[N-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine]
(**10b**, $C_{28}H_{27}Cl_2N_7O_3$)
Prepared similarly to **9b** from 1.232 g **4b** (2 mmol). Recrystallization from DMF–H_2O afforded 0.99 g (86%) **10b**. M.p.: 221–222 °C; ^{1}H NMR: $\delta = 1.29$ (t, 3H, $J = 6.9$ Hz, CH_3CH_2O), 2.38 (t, 4H, $J = 7.2$ Hz, $CH_2C{=}N$), 3.67 (t, 4H, $J = 6.9$ Hz, CH_2N), 3.93 (q, 2H, $J = 6.9$ Hz, CH_3CH_2O), 7.27–7.34 (m, 4H, H–Ar), 7.48–7.67 (m, 8H, H–Ar′), 8.84, 9.42 (2s, 2H, NH) ppm; ^{13}C NMR: $\delta = 153.44$ (C-10), 148.55 (C-4), 138.53 (C-9), 138.27 (C-1), 128.37 (C-11), 128.21 (C-14), 125.53 (C-13, 15), 119.89 (C-12, 16), 115.20 (C-2, 6), 114.48 (C-3, 5), 63.25 (C-17), 47.53 (C-7), 24.82 (C-8), 17.08 (C-18) ppm; MS (20 eV): *m/z* (%) = 581 ($[M + H]^+$, 100).

5,5′-[[(4-Methoxyphenyl)imino]diethane-2,1-diyl]bis-(N-phenyl-1,3,4-thiadiazol-2-amine)
(**11a**, $C_{27}H_{27}N_7OS_2$)
Prepared similarly to **9a** from 0.23 g **5a** (0.4 mmol). Recrystallization from DMF–H_2O afforded 0.11 g (51%) **11a**. M.p.: 114–115 °C; ^{1}H NMR: $\delta = 3.09$ (t, 4H, $J = 6.9$ Hz, CH_2CO), 3.73 (s, 3H, CH_3O), 3.86 (t, 4H, $J = 6.9$ Hz, CH_2N), 6.99 (d, 2H, $J = 9$ Hz, $H_{(2,6)}Ar$), 7.24 (d, 2H, $J = 9$ Hz, $H_{(3,5)}Ar$), 7.32 (m, 6H, $H_{(3,4,5)}Ar'$), 7.58 (d, 4H, $J = 7.5$ Hz, $H_{(2,6)}Ar'$), 10.32 (br s, 2H, NH) ppm; ^{13}C NMR: $\delta = 164.58$ (C-10), 162.31 (C-9), 155.93 (C-4), 140.56 (C-1), 127.77 (C-11), 129.04 (C-14), 124.05 (C-13, 15), 121.78 (C-2, 6), 117.28 (C-12, 16), 115.11 (C-3, 5), 55.51 (C-17), 53.03 (C-7), 26.33 (C-8) ppm; IR (KBr): $\bar{\nu}$ = 3,289 (NH), 1,431 (C=N) cm^{-1}; MS (20 eV): *m/z* (%) = 530 ($[M + H]^+$, 70).

5,5′-[[(4-Ethoxyphenyl)imino]diethane-2,1-diyl]bis-(N-phenyl-1,3,4-thiadiazol-2-amine)
(**11b**, $C_{28}H_{29}N_7OS_2$)
Prepared similarly to **11a** from 1.45 g **5b** (2.5 mmol). Recrystallization from DMF–H_2O afforded 0.88 g (65%) **11b**. M.p.: 170–171 °C; ^{1}H NMR: $\delta = 1.24$ (t, 3H, $J = 6.9$ Hz, CH_3CH_2O), 2.47 (t, 4H, $J = 7.2$ Hz, CH_2CS), 3.14 (t, 4H, $J = 7.2$ Hz, CH_2N), 3.83 (q, 2H, $J = 6.9$ Hz, CH_3CH_2O), 6.49 (d, 2H, $J = 9.2$ Hz, $H_{(2,6)}Ar$), 7.15 (d, 2H, $J = 9.2$ Hz, $H_{(3,5)}Ar$), 7.21 (t, 2H, $J = 7.2$ Hz, $H_{(4)}Ar'$), 7.39–7.54 (m, 8H, $H_{(2,3,5,6)}Ar'$), 8.66 (s, 2H, $NHAr'$) ppm; IR (KBr): $\bar{\nu} = 3{,}290$ (NH), 1,432 (C=N) cm^{-1}; MS (20 eV): *m/z* (%) = 544 ($[M + H]^+$, 80).

References

1. Shehata A (2003) Saudi Pharm J 11:87
2. Mekuskiene G, Tumkevicius S, Vainilavicius P (2002) J Chem Res (S) 213
3. El-Massy AH, Fahmy HH, Abdelwahed SHA (2000) Molecules 5:1429
4. Tumosienė I, Kantminienė K, Pavilonis A, Maželienė Ž, Beresnevičius ZJ (2009) Heterocycles 78:59
5. Wujec M, Pitucha M, Dobosz M, Kosikowska U, Malm A (2004) Acta Pharm 54:251
6. Beresnevičius ZJ, Viliūnas V, Kantminienė K (2000) Chem Heterocycl Comp 36:504
7. Mickevicius M, Mickevicius V, Beresnevicius ZJ, Jakiene E (2005) Chem Technol 3(37):50
8. Tumosienė I, Jakienė E, Beresnevičius ZJ, Mikulskienė G (2006) Chem Technol 3(41):58
9. Dawood KM, Farag AM, Abdel-Aziz HA (2005) Heteroat Chem 16(7):621